CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-701

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

CRINONE[R]
PROGESTERONE VAGINAL GEL

NDA 20-701

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
(HFD-580)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-701

CRINONE[R]

PROGESTERONE VAGINAL GEL

VAGINAL GEL

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **CRINONE[R], Columbia Research Laboratories, Inc.** has prepared an environmental assessment (attached) according to 21 CFR 25.31a and Tier 0 appproach which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Progesterone is a chemically synthesized drug which is incorporated into a gel for treatment of secondary amenorrhea and abnormal bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. The drug substance will be manufactured by Appropriate environmental compliance certification is included .

The bulk drug product (gel) will be manufactured by The bulk gel will be packaged into unit dose package at The appropriate licenses from the foreign authorities were attached. The finished drug product will be used by consumers all over the United States.

The human metabolism and disposition of progesterone have been well characterized.

Progesterone and its metabolites from consumer use would be expected to enter the aquatic environment.Progesterone is a naturally-occurring substance in the environment as a result of normal excretion by animals and humans. It is predicted that use of Crinone[R] would not

reasonably be expected to alter pre-existing environmental concentrations or distribution of progesteronel and its metabolites.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and drug products will be disposed at the foreign facilities indicated above. The returned drug products will be disposed of in a solid waste management system in the US. The hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drugs may be disposed of in the sewer system.

The center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

5-9-97
DATE

PREPARED BY
Dr. Amit K. Mitra
Review Chemist, HFD-580
Reproductive and Urologic Drug Products

5/9/97
DATE

DIVISION CONCURRENCE
Dr. Moo-Jhong Rhee
Chemistry Team Leader
HFD-820 assigned to HFD-580

5/13/97
DATE

CONCURRED/
Nancy B. Sager
Team Leader
Environmental Assessment Team, HFD-357
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet (drug substance)
EA submitted by the applicant

CC: Original NDA 20-701
HFD-580/Division file
HFD-580/A. Mitra
HFD-580/M.J.Rhee
HFD-580/D. Moore
HFD-357/FONSI File/NDA 20-701
HFD-357/Docket File
HFD-205/FOI Copy

3.12 Environmental Assessment

3.12 Environmental Assessment

This environmental assessment (EA) was prepared using the November, 1995 CDER Guidance document entitled, "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements." The Tier 0 approach is being used due to the expected introduction concentration from use (EIC) being <1 ppb (refer to Section 3.12.6). Therefore, as indicated in the guidance document, an abbreviated environmental assessment has been prepared.

3.12.1 Date

This EA was prepared on July 9, 1996.

3.12.2 Applicant

The applicant for this NDA is Columbia Research Laboratories, Inc.

3.12.3 Address for Correspondence

All correspondence should be addressed to:

Columbia Research Laboratories, Inc.
100 No. Village Avenue
Rockville Center, NY 11570

3.12.4 Description of the Proposed Action

A. Requested Approval

Columbia Research Laboratories, Inc. Has filed NDA 20-701 for CRINONE® (progesterone gel), 8% and 4% strengths, packaged in single-use, one piece polyethylene vaginal applicators. An abbreviated EA has been submitted pursuant to 21 CFR §25.31a(a)&(b).

B. Need for Action

CRINONE® is intended to be used in the treatment of:

- secondary amenorrhea
- abnormal bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer.

This is accomplished by the extended-release nature of the formulation which, when administered vaginally (i.e., locally) in the presence of adequate estrogen, transforms a proliferative endometrium into a secretory endometrium.

C. Production Locations

The drug substance, progesterone, will be manufactured by:

Manufacturer:

The facility is located in an industrial area, which has a temperate climate. The facility is not in the vicinity of a river, lake, mountain, or forest.

The bulk progesterone gel will be manufactured by:

The facility is located in a residential area, which has a temperate climate. It is situated approximately one-half mile from a river. A copy of the site description has been provided in the Appendix (Section 3.12.15).

The bulk gel is filled into applicators and the applicators individually wrapped by:

The facility is located in an industrial area, which has a temperate, continental climate. The facility is surrounded by hills.

D. Locations of Use

It is intended that CRINONE® be used primarily by patients in their homes. There is no expectation that use will be concentrated in a particular geographic area.

E. Disposal Sites

The method of disposal of rejected, expired or waste drug product is in keeping with the current practices of Additional information on the manufacturing and control of the drug substance can be found in DMF A copy of the DMF authorization letter is provided in the Appendix (refer to Section 3.12.15).

The method of disposal of rejected, expired or waste bulk drug substance is in keeping with current practices of has been issued a manufacturer's license #ML/9394/1 from the Medicines Control Agency (MCA). A copy of the license in provided in the Appendix (refer to Section 3.12.15). Additional environmental information is provided as well.

The method of disposal of rejected, expired or waste finished drug product in is keeping with the current practices of was granted permission for the filling of drugs, including sterile preparations, from the A copy of the permit (original plus the translation) is provided in the Appendix (refer to Section 3.12.15). Please note that the permit is due to be renewed in September-October, 1996.

Although it is not anticipated that there will be much use in U.S. hospitals, pharmacies or clinics, empty or partially empty containers will be disposed of according to their procedures. In the home, empty or partially empty containers will be disposed of in the community's solid waste management system which may include landfills or incineration.

3.12.5 Identification of the Chemical Substance (Drug Substance) that is the Subject of the Proposed Action

A. Nomenclature

I.	USAN Name		Progesterone
II.	Brand Name		N/A
III.	Chemical Names		
	(1)	Chemical Abstracts Name	Progesterone
	(2)	Systematic Chemical Name	Pregn-4-ene-3,20-dione

B. Chemical Abstracts Service (CAS) Registration Number

CAS-57-83-0

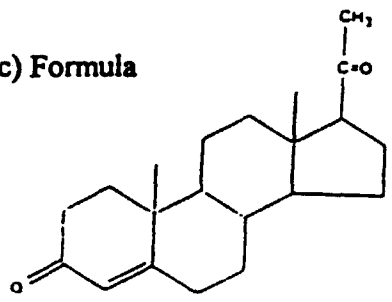
C. Molecular Formula

$C_{21}H_{30}O_2$

D. Molecular Weight

314.47

E. Structural (graphic) Formula



F. Description

White to creamy white, odorless crystalline powder

G. Additives

The following table lists the Statement of Composition for the final formulation and the CAS Registry Numbers of each component.

CRINONE® Statement of Composition						
Component	45 mg (4%)		90 mg (8%)		Function	CAS Registration Number
	mg/dose	% w/w	mg/dose	% w/w		
Progesterone (micronized)	45.00	4.0	90.00	8.0	Active Ingredient	57-83-0
Glycerin						56-81-5
						8012-95-1
Hydrogenated Palm Oil Glyceride						*
Carbomer 934						9003-01-4
Sorbic Acid						110-44-1
Polycarbophil						9003-97-8
Sodium Hydroxide						1310-73-2
Purified Water						7732-18-5

Notes: Commercial names are given in parentheses
Each applicator delivers a dose of 1.125 g gel

* = An MSDS for this product is provided in the Appendix (refer to Section 3.12.15)

H. Impurities

Information on the impurities potentially involved with the manufacturing of progesterone can be found in DMF

3.12.6 Introduction of Substances into the Environment

All activities associated with the production of the drug substance and drug product are carried out outside the U.S. Certification information from the manufacturer of the drug substance, is provided in the Appendix (Section 3.12.15) Acknowledgments from the local authorities concerning their awareness of the drug product manufacturing/packaging operations at the respective facilities can be found in the license and accompanying environmental documentation and the registration documentation in the Appendix (Section 3.12.15). Therefore, Sections 3.12.6.a-e are not applicable.

Calculation of the Expected Introduction Concentration from Use/Justification for Tier 0

The EIC calculation is based on the fifth year production and assumes that all drug product produced is evenly distributed throughout the U.S. per day, and there are no metabolism and depletion mechanisms. It should be noted that the drug substance, progesterone, is a naturally produced human hormone and is already entering the environment via the publicly owned treatment works (POTW).

EIC-Aquatic (ppm) = A x B x C x D

Where A = 4000 kg/year

B = 1/liter per day entering POTWs

C = year/365 days

D = 10^6 mg/kg

EIC-Aquatic (ppm) = 0.00017 ppm = 0.17 ppb (<1ppb)

3.12.7 - 3.12.11

Not applicable due to the Tier 0 requirement being met.

3.12.12 List of Preparers

This EA was prepared by Barbara M. Finn, Director of Regulatory Operations,

A copy of her CV is provided in the Appendix (refer to Section 3.12.15).

3.12.13 Certification

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm responsible for the preparation of the EA.

The undersigned official certifies that the EA summary document (pages 223-229) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR §1506.6.

Howard Levine, Pharm D.
Vice President
Columbia Research Laboratories

3.12.14 Not applicable due to the Tier 0 requirement being met.

3.12.15 Appendices (Confidential)

AKZO NOBEL

SAFETY DATA SHEET

according to EC-directive 93/112/EC

PROGESTERONE

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

Chemical identity	Pregn-4-ene-3,20-dione. Pregnenedione. Progesteronum.
CAS-number	57-83-0
EINECS/ELINCS	200-350-6
Formula	$C_{21}H_{30}O_2$
Supplier	DIOSYNTH B.V., P.O. BOX 20, 5340 BH OSS, THE NETHERLANDS
Telephone	+31 (0)412-661333 NL
Emergency telephone	+31 (0)412-661600 NL

2. COMPOSITION/INFORMATION ON INGREDIENTS

This product is to be considered a substance in conformance with EC directives.

3. HAZARDS IDENTIFICATION

Harmful by inhalation, in contact with skin and if swallowed. Possible risks of irreversible effects. May cause sensitization by inhalation and skin contact.

4. FIRST AID MEASURES

Therapeutical category	Progestogens
BGD-code	1515
Routes of exposure	Inhalation, ingestion, mucous membrane absorption and skin absorption.
Symptoms and effects	Effects of overexposure: Harmful by inhalation, in contact with skin and if swallowed. Effects as for progestogens in general. In female: amenorrhoea, Changes in libido. Impaired glucose tolerance. Reversible gynaecomastia in male. Effects on fertility. Effects on menstruation. Symptoms of exposure may include: headache, dizziness, gastro-intestinal complaints, nausea and vomiting, water and sodium retention. Additional remarks: May cause sensitization by inhalation and skin contact. Allergic reactions may occur.
First aid	
General	In all cases of doubt, or when symptoms persist, seek medical attention.
Inhalation	Remove from exposure, fresh air, rest, if breathing is difficult, give oxygen. Obtain medical attention immediately (show this Material Safety Data Sheet).

Storage requirements	Store in well closed containers protected from light and moisture, at 15-25 °C .
Other information	Do not eat, drink or smoke in application area. Keep working clothes separately and do not take them home.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Engineering controls	Ensure good ventilation and local exhaust ventilation of the working area. If these measures are not sufficient, suitable respiratory protection must be worn.
Exposure limits	No exposure limit has been established.
Personal protection	
Respiratory	Use appropriate breathing apparatus.
Hand	Wear suitable gloves.
Eye	Wear safety goggles.
Skin and body	Wear suitable protective clothing: special overalls, tight fitting at neck, ankles and wrists and head covered. Change daily. Take a shower at the end of the workday.
Other information	-

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	crystalline powder
Colour	white to almost white
Odour	odourless
Boiling point/range	not applicable
Melting point/range	120-130 °C
Flash point	not applicable
Flammability	not applicable
Auto-ignition temperature	not applicable
Explosive properties	not applicable
Explosion limits	not applicable
Oxidizing properties	not applicable
Vapour pressure	not applicable
Density	not determined
Bulk density	not determined

Solubility in water	insoluble in water
Solubility in other solvents	soluble in alcohol 1:8, chloroform 1:<1, slightly soluble in acetone, ether, dioxane and vegetable oils
pH value	not applicable
Partition coefficient n-octanol/water	not determined
Relative vapour density air = 1	not applicable
Viscosity	not applicable
SADT	not applicable
Specific conductivity	not applicable
Other information	-

10. STABILITY AND REACTIVITY

Stability	Stable under recommended storage and handling conditions (see section 7).
Conditions to avoid	None.
Materials to avoid	None.
Hazardous decomposition products	None.
Other information	-

11. TOXICOLOGICAL INFORMATION

Acute toxicity	
Oral LD50	No data available.
Dermal LD50	No data available.
Inhalation LC50	No data available.
Irritation	
Skin	No data available.
Eye	No data available
Respiratory	No data available
Sensitization	No data available.
Genotoxicity	Possible risks of irreversible effects: experimental neoplastigen, carcinogen and tumorigen. Mutagenic data. Sufficient evidence of carcinogenicity in experimental animal (IARC). Progestogens: Inadequate evidence of carcinogenicity in human (IARC). The group as a whole is classified as possibly carcinogenic to human, this may not apply to all individual substances within the group.

Other toxicological information	Acute toxicity: ori-rat LD50: > 6400 mg/kg (MEDROXYPROGESTERONE ACETATE). ivn-mouse LD50: 100 mg/kg. Chronic toxicity: no chronic toxicity data available. Reproductive effects: experimental teratogen, reproductive disorder(s) in human and experimental animal. ori-woman TDLo: 100 mg/kg (20 day(s) pre-mating), ori-rat TDLo: 25 mg/kg (female, 1 day(s) pre-mating), ims-man TDLo: 15 mg/kg (21 day(s) pre-mating), scu-rat TDLo: 500 10^{-3}mg/kg (female, 2 day(s) pre-mating). RTECS No. TW0175000; N.I. Sax et al. (7Ed), 1989, p 2880; Martindale "The Extra Pharmacopoeia" (30Ed), J.E.F. Reynolds, 1993, p 1170&1194; IARC Monographs, Volume 50, 1990; IARC Monographs Suppl.7, 1987. RTECS No. TU5010000 (MEDROXYPROGESTERONE ACETATE).

12. ECOLOGICAL INFORMATION

No data available.

13. DISPOSAL CONSIDERATIONS

Product	According to local regulations: controlled incineration, controlled landfill.
Contaminated packaging	According to local regulations: controlled incineration, controlled landfill.
Other information	Non-contaminated containers can be treated like domestic garbage. According to local regulations.

14. TRANSPORT INFORMATION

Land transport

ADR class	ADR item number
RID class	RID item number
Hazard Identification No.	Substance Identification No.
TREM-Card	UN number
Proper shipping name	
Other information	No dangerous good, according to national and international transport regulations.

Sea transport

UN number	Class

Packing group	Marine pollutant
EMS	MFAG
Proper shipping name	
Other information	No dangerous good, according to national and international transport regulations.

Air transport

IATA/ICAO-DGR	UN number
Class	Packing group
Proper shipping name	
Other information	No dangerous good, according to national and international transport regulations.

15. REGULATORY INFORMATION

Labelling according to	EU directives and own criteria.
EU-number	200-350-6
Symbol(s)	 Xn HARMFUL
R(isk) phrase(s)	R20/21/22: Harmful by inhalation, in contact with skin and if swallowed. R40: Possible risks of irreversible effects. R42/43: May cause sensitization by inhalation and skin contact.
S(afety) phrase(s)	S36/37: Wear suitable protective clothing and gloves. S38: In case of insufficient ventilation, wear suitable respiratory equipment. S44: If you feel unwell, seek medical advice (show the label where possible).
Other information	Micro crystalline powder, with S22: Do not breathe dust.

16. OTHER INFORMATION

This information only concerns the above mentioned product and does not need to be valid if used with other product(s) or in any process. The information is correct and complete to our best present knowledge and is given in good faith, but without warranty. It remains the user's own responsibility to make sure that the information is appropriate and complete for his special use of this product.

History

AKZO NOBEL

SAFETY DATA SHEET

According to EC-directive 93/112/EC

PROGESTERONE

Date of printing	23/05/1996
Revision	01
Composed by	Dept. of Safety and Environmental Affairs
Changes were made in section	1, 7, 8, 9

MOORE

MAY - 9 1997

NDA 20-701 Crinone® (Progesterone vaginal gel)
Amendment: BC

ENVIRONMENTAL ASSESSMENT

1. Date:
EA submitted on: 23 July, 1996
EA Amendment submitted on: 19 April, 1997
NDA submitted on: 23 July, 1996

2/3 Name/Address of the Applicant:
Columbia Research Laboratories, Inc.
100 No. Village Avenue
Rockville Center, NY 11570

Crinone® in application NDA 20-701 is intended to be used in treatment of secondary amenorrhoea, abnormal bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids and uterine cancer. NDA 20-701 contains all environmental assessment related information for Crinone® and progesterone. A separate confidential section was provided by the sponsor in section 3.12.15 of volume 5 of the NDA.

An amendment to this NDA was submitted on April 19, 1997 to include:1. MSDS sheet for progesterone as provided by the supplier, 2. Procedure for disposal of returned and damaged goods at Columbia; 3. Appropriate signature at page 229 of section 3.12.

Progesterone is a naturally occurring substance in the environment as a result of normal excretion by humans, livestock and other domesticated animals, and wildlife. Therefore the sponsor has provided an abbreviated environmental assessment according to 21 CFR 25.31a with Tier 0 approach. Since progesterone is a naturally occurring substance (produced endogenously) and EIC is less than 1 ppb, only an abbreviated environmental assessment is needed according to the Guidance to Industry for Submission of Environmental Assessment in Human Drug Applications and Supplements.

4. Description of the proposed action
a. Requested Approval
Commercial distribution of the product in the United States. The product contains 4 or 8% progesterone. Other than progesterone, the drug products contain glycerin, hydrogenated palm oil, carbomer 934, sorbic acid, polycarbophil, sodium hydroxide and purified water

b. Need for Action
The progesterone transdermal gel is indicated for secondary amenorrhea and abnormal bleeding due to hormonal imbalance in the absence of

organic pathology, such as fibroids or uterine cancer.

This section is satisfactory.
c. Location of Production
The bulk drug substance progesterone is obtained from

has provided the following information:

1. Documents from the provincial authorities titled "Adequate Environmental Licenses".
2. Statement from the Dike Council of the Waterboard "The Maaskant".
4. Material Safety Data Sheet for progesterone and hydrogenated palm oil.

The bulk gel drug product is manufactured by:

The facility is located in a residential area. It is situated approximately ½ mile from a river. A copy of the site description is provided.

The manufacturing license for and additional environmental information for the site were provided.

The bulk gel is packaged in unit dose packages by

Permit for packaging by the Department of Health (local government) is provided.

This section is satisfactory.

d. Location of use: The product will be used in homes, clinics, and hospitals all over the United States. There is no expectation that use will be concentrated in a particular geographic area.
This section is satisfactory.

e. Disposal sites: Crinone manufacturing and packaging occurs outside the United States. Copies of license and permits from foreign governments were provided. Drug product will be used in the US. The empty container and unused product will be disposed of in community's solid waste management system which may include landfills or incineration. Drug products returned to Columbia Laboratories after entry into the United States will be disposed of in a solid waste management system. Columbia laboratories is in the process of identifying a site for return in the United States.
This section is satisfactory.

5. Identification of Chemical Substances that are the Subject of the Proposed Action

The active chemical is progesterone which is a naturally occurring substance. The drug is chemically known as Pregn-4-ene-3,20-dione. structural formula: $C_{21}H_{30}O_2$, Molecular Weight: 314.47.

The drug substance progesterone is a white to creamy white, oderless crystalline powder and it was cross referenced to DMF The potential impurities were also cross-referenced to the DMF The DMF is being reviewed.

This section is satisfactory.

Description of Drug Product was also given. This application is for 4 and 8% gels. The additives (excipients) in the drug product are glycerin, . hydrogenated palm oil glyceride, carbomer 934, sorbic acid, polycarbophil, sodium hydroxide and purified water.

6. Introduction of Substances into the Environment

The active drug is synthesized by . Other than the active drug substance, the drug products contain glycerin, hydrogenated palm oil, carbomer 934, sorbic acid, polycarbophil, sodium hydroxide and purified water. All ingredients are compendial except hydrogenated palm oil. MSDS of the active drug and hydrogenated palm oil were provided Manufacturing and packaging operation will be conducted at outside the US as mentioned below.

Crinone will be used and disposed all over the US. Patients will dispose of used unit dose packages in household trash. The rejected goods will be handled by facilities outside the US. The returned goods at Columbia Laboratories will be incinerated by a licensed contractor at Columbia Laboratories in the US.

Progesterone drug substance is manufactured in the as indicated above. The manufacturing information for progesterone is documented in the DMF . The company is in compliance with appropriate environmental regulation in This is satisfactory.

The drug product (Crinone bulk gel) is manufactured by

The bulk gel is packaged by
The components of Crinone is given above. The substances which may potentially be released to the environment through manufacturing and packaging of Crinone is under the jurisdiction of foreign authorities; therefore it is not covered here.

Introduction of substances from the use and disposal of Crinone:

There are three possible sources: 1. Excretion of the progesterone, or other ingredients and metabolites following the use of the product. 2. Disposal of unused gels by patient, pharmacies and distributors. Those will be finally in landfill or would be incinerated. The calculated EIC is 9.8×10^{-2} ppb.

EXPECTED INTRODUCTION CONCENTRATION FROM USE:
EIC- Aquatic (ppm) = A x B x C x D
Where A= kg/year production = 4,000 kg
B= 1/ liters/day entering POTW's
C= year/365 days
D= 10^6 mg/kg

EIC (ppm) = $4000 \times 10^6 / 1.115 \times 365 \times 10^{11} = 9.8 \times 10^{-5}$
EIC (ppb) =0.098 ppb

This section is satisfactory.

7. Fate of Emitted Substances in the Environment
Not needed for Tier 0

8. Environmental Effects of Released Substances
Not needed for Tier 0.

9. Use of Resource and Energy
Not needed for Tier 0

10. Mitigation Measures
Not needed in Tier 0.

11. Alternatives to the Proposed Action
Not needed in Tier 0.

12. List of Preparers
Preparer was identified, and her qualification was provided.

13. Certification
Certification was provided

14. References
None provided

15. Appendices
MSDS's and other confidential information cited in the assessment were provided.

Reviewer's Conclusion and Recommendation:
The environmental Assessment is satisfactory and a FONSI can be prepared for the NDA

Amit K. Mitra, Ph.D

cc:
Orig. NDA 20-701
HFD-580/Division File
HFD-580/A. K. Mitra/5-10-97
HFD-580/D. Moore
HFD-580/ M.J. Rhee
R/D Init By: 5/9/97